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Homocysteine aggravates ROS-induced depression of transmitter release from motor nerve terminals: Potential mechanism of peripheral impairment in motor neuron diseases associated with hyperhomocysteinemia

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Abstract

© 2015 Bukharaeva, Shakirzyanova, Khuzakhmetova, Sitdikova and Giniatullin. Homocysteine (HCY) is a pro-inflammatory sulphur-containing redox active endogenous amino acid, which concentration increases in neurodegenerative disorders including amyotrophic lateral sclerosis (ALS). A widely held view suggests that HCY could contribute to neurodegeneration via promotion of oxidative stress. However, the action of HCY on motor nerve terminals has not been investigated so far. We previously reported that oxidative stress inhibited synaptic transmission at the neuromuscular junction, targeting primarily the motor nerve terminals. In the current study, we investigated the effect of HCY on oxidative stress-induced impairment of transmitter release at the mouse diaphragm muscle. The mild oxidant H2O2 decreased the intensity of spontaneous quantum release from nerve terminals (measured as the frequency of miniature endplate potentials, MEPPs) without changes in the amplitude of MEPPs, indicating a presynaptic effect. Pre-treatment with HCY for 2 h only slightly affected both amplitude and frequency of MEPPs but increased the inhibitory potency of H2O2 almost two fold. As HCY can activate certain subtypes of glutamate N-methyl Daspartate (NMDA) receptors we tested the role of NMDA receptors in the sensitizing action of HCY. Remarkably, the selective blocker of NMDA receptors, AP-5 completely removed the sensitizing effect of HCY on the H2O2-induced presynaptic depressant effect. Thus, at the mammalian neuromuscular junction HCY largely increases the inhibitory effect of oxidative stress on transmitter release, via NMDA receptors activation. This combined effect of HCY and local oxidative stress can specifically contribute to the damage of presynaptic terminals in neurodegenerative motoneuron diseases, including ALS.

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Keywords

Amyotrophic lateral sclerosis, Homocysteine, Neuromuscular junction, NMDA receptors, Oxidative stress